Klebsiella Species Infections in the Department of the Navy (DON) and Department of Defense (DOD): Annual Report 2014

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14. ABSTRACT

Gram-negative Klebsiella bacterial infections are of growing global public health and clinical concern. Epidemics of multidrug-resistant (MDR) gram-negative bacteria, including Klebsiella species, have occurred worldwide in the last two decades, including regions where United States (US) military forces are regularly deployed. In 2014, the incidence of all Klebsiella spp. infections increased to 83.6 cases per 100,000 eligible beneficiaries from 63.0 cases per 100,000 eligible beneficiaries in 2013 among Department of the Navy (DON) and Department of Defense (DOD) beneficiaries seeking care in the Military Health System (MHS). A pronounced gender disparity was observed for Klebsiella spp. infections; overall, DON and DOD female beneficiaries were infected more than four times as often as males. Within the MHS, Klebsiella spp. cases commonly manifested as urinary tract infections (UTIs), which was consistent with previous analysis. MDR Klebsiella spp. infections accounted for less than 5% of all Klebsiella spp. infections. Females over the age of 45 had the highest rates of MDR infections. Compared to non-MDR Klebsiella spp. infections, a higher percentage of MDR infections were healthcare-associated. Klebsiella spp. infections remained susceptible to many antibiotic classes, such as carbapenems, sulfonamides, fluoroquinolones, and cephalosporins; ciprofloxacin was the most commonly prescribed antibiotic. MDR

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Abstract

Gram-negative *Klebsiella* bacterial infections are of growing global public health and clinical concern. Epidemics of multidrug-resistant (MDR) gram-negative bacteria, including *Klebsiella* species, have occurred worldwide in the last two decades, including regions where United States (US) military forces are regularly deployed. In 2014, the incidence of all *Klebsiella* spp. infections increased to 83.6 cases per 100,000 eligible beneficiaries from 63.0 cases per 100,000 eligible beneficiaries in 2013 among Department of the Navy (DON) and Department of Defense (DOD) beneficiaries seeking care in the Military Health System (MHS). A pronounced gender disparity was observed for *Klebsiella* spp. infections; overall, DON and DOD female beneficiaries were infected more than four times as often as males. Within the MHS, *Klebsiella* spp. cases commonly manifested as urinary tract infections (UTIs), which was consistent with previous analysis. MDR *Klebsiella* spp. infections accounted for less than 5% of all *Klebsiella* spp. infections. Females over the age of 45 had the highest rates of MDR infections. Compared to non-MDR *Klebsiella* spp. infections, a higher percentage of MDR infections were healthcare-associated. *Klebsiella* spp. infections remained susceptible to many antibiotic classes, such as carbapenems, sulfonamides, fluoroquinolones, and cephalosporins; ciprofloxacin was the most commonly prescribed antibiotic. MDR *Klebsiella* spp. infections were least resistant to carbapenems.

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Executive Summary

The EpiData Center Department (EDC) at the Navy and Marine Corps Public Health Center (NMCPHC) conducts routine surveillance of clinically significant organisms within the Department of the Navy (DON) and the Department of Defense (DOD). This report provides a summary of the incidence and prevalence of *Klebsiella* species and multidrug-resistant (MDR) *Klebsiella* spp. infections in calendar year (CY) 2014. Separate analyses were conducted among populations of interest, including all DOD beneficiaries, active duty DON service members, deployed DON service members, and DON recruits. The report includes details on case demographics, clinical infection characteristics, prescription practices, and antibiotic resistance patterns.

The linking of several data sources in this analysis allowed for a comprehensive assessment of a variety of unique descriptive and clinical factors related to *Klebsiella* spp. infection within multiple populations in the Military Health System (MHS). Health Level 7 (HL7) formatted microbiology data from MHS facilities were used to identify all *Klebsiella* spp. isolates. The isolates were matched to three databases: (1) HL7 formatted pharmacy data to assess prescription practices associated with *Klebsiella* spp.; (2) Standard Inpatient Data Record (SIDR) database to determine hospital exposure associations within the MHS; and (3) the Defense Manpower Data Center (DMDC) personnel roster to determine the burden of *Klebsiella* spp. infection among active duty DON service members and recruits.

This analysis found that during CY 2014, *Klebsiella* spp. infections increased in incidence and prevalence in the DON and DOD compared to 2005-2013 rates within MHS. Demographic profiles followed previously observed trends, with high incidence observed among adult females and a high prevalence of urinary tract infections (UTIs) among *Klebsiella* spp. cases. Overall, low frequencies of multidrug-resistance were observed among the populations within this report. Continued monitoring of the disease dynamics will help military healthcare providers prepare for the evolving resistance and burden of *Klebsiella* spp. infections in the MHS and identify effective treatment, prevention, and infection control programs.

Introduction

Gram-negative bacterial infections caused by organisms in the genus *Klebsiella,* from the family Enterobacteriaceae, are a growing problem in both the general global population and among US military service members. In the US, *Klebsiella* species are among the most clinically significant organisms associated with a variety of diseases, including cystitis, pneumonia, and bacteremia, and are estimated to cause eight percent of all nosocomial infections.[1]

Klebsiella spp. have the ability to harbor different mechanisms of resistance, enabling many commonly used antibiotics to be ineffective. These MDR *Klebsiella* infections have significantly impacted medical communities on the global scale and often leave only last resort antibiotics as treatment options. In recent decades, carbapenems were used with increased frequency as one of the few effective treatment options against drug-resistant, gram-negative organisms.[2] In the early 2000s, resistance to carbapenems emerged among Enterobacteriaceae. Carbapenem-resistant enterobacteriaceae (CRE) are unique among multidrug-resistant organisms (MDROs) because there are no reliable treatments to combat them, resulting in wide-ranging global public health implications. CREs are frequently caused by the production of *Klebsiella pneumoniae* carbapenemase (KPC), commonly identified in *K. pneumoniae* isolates.[3] Furthermore, bacteria with carbapenem-resistant genes typically confer resistance to additional antibiotic classes, resulting in a wide range of resistance patterns including extensively drug-resistant (XDR) organisms, which are described below.[2] It has been reported that in US hospitals, the percentage of carbapenem-resistant *K. pneumoniae* has increased from <1% in 2000 to 8% in 2006-2007 to 12% in 2009-2010.[4] According to the Centers for Disease Control and Prevention (CDC), in February 2015 CREs were reported in 48 US states and endemic in South America, Europe, Africa, and Asia.[4,5] The impact of MDR *Klebsiella* bacteria in community and hospital settings is cause for concern.

During Operation Iraqi Freedom and Operation Enduring Freedom (OIF/OEF), a large number of resistant gram-negative bacteria were identified in US combat support hospitals. The USNS *Comfort* also reported infections at the beginning of OIF. In the early days of the conflicts, these infections were observed primarily in non-US patients and although the proportion of *Klebsiella* infections among all infections was small (6%), the isolates were highly resistant to third-generation cephalosporins.[6] However, between 2002 and 2005, antibiotic resistant *Klebsiella pneumoniae* infections among service members injured in OIF/OEF were identified with increased frequency, and one military treatment facility (MTF) found antibiotic resistance in nearly all agents tested.[7,8]

In 2001, Jones et al. reported that nosocomial infections account for more than 77,000 deaths per year in the US, costing $5-$10 billion annually.[9] While gram-positive organisms have typically been the most frequent cause of nosocomial infections and continue to be of concern, gram-negative organisms have emerged with resistance at troubling rates.[9] In intensive care units, gram-negative bacteria have been identified, to varying degrees, as a frequent cause of the four most common types of healthcare-associated infections (HAIs): nosocomial pneumonia, UTIs, surgical site infections (SSIs), and blood stream infections (BSIs).[10] In 2003, among voluntarily

participating US hospital intensive care units, *K. pneumoniae* was implicated in 7.2% of nosocomial pneumonia cases, 4.2% of BSIs, 3.0% of SSIs, and 9.8% of UTIs.[10]

Another study assessing data from 2009-2010, reported 8% of HAIs were due to *Klebsiella* spp., with approximately 2% extended-spectrum cephalosporin-resistant and less than 1% carbapenem-resistant.[11] Most antibiotic-resistant HAIs are preventable. Endemic, rather than epidemic, problems represent the majority of HAIs. Therefore, routine surveillance is a necessary infection control tool to aid in the prevention of HAIs and containment of MDR pathogens, such as *Klebsiella*. The Society for Healthcare Epidemiology of America and the Hospital Infection Control Practices Advisory Committee (SHEA/HICPAC) developed several metrics recommended for the surveillance of HAIs. Exposure burden is an important metric for detecting importation of MDROs into the healthcare facility that potentially serves as a reservoir for HAIs.[12] Infection burden metrics can be used to assess the overall organism-specific and device- or procedure-associated incidence. Both sets of metrics can be used to track changes over time and direct prevention efforts.

This report is a retrospective analysis of *Klebsiella* spp. infections among DON and DOD beneficiaries in CY 2014. This update compares the 2014 incidence to historical trends established from 2005 – 2013 in the DON and DOD as a reference for assessing the current year's burden.

Methods

Study Design, Setting, and Population

This is a retrospective surveillance summary for CY 2014 to assess the incidence, prevalence, and trends of *Klebsiella* species infections among DON and DOD beneficiaries. HL7 formatted microbiology data that originated from the Composite Health Care System (CHCS) at fixed MTFs were used to identify all *Klebsiella* cases for DOD beneficiaries who sought care within the MHS in 2014. *Klebsiella* infection within this report will refer to the identification of: *K. pneumoniae*, *K. oxytoca*, *K. ozaenae*, or *Klebsiella* spp.. The EDC assessed all outpatient and inpatient isolates as determined by the Medical Expense and Performance Reporting System (MEPRS) codes in microbiology data. A MEPRS code beginning with 'A' indicated specimen collection in the inpatient setting while all other codes were considered outpatient.

Antibiotic susceptibility results from the microbiology record were used to establish the level of antibiotic resistance among cases. Isolates non-susceptible (resistant or intermediately susceptible) to at least one antibiotic in at least three different classes were considered MDR. The antibiotic classes considered in this analysis include select cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, folate pathway inhibitors, glycylcyclines, monobactams, phenicols, phosphoric acids, penicillins and β-lactamase inhibitor combinations, polymyxins, and tetracyclines. Organisms non-susceptible to at least one antibiotic in all but one or two classes were considered XDR. Finally, PDR organisms were organisms that were non-susceptible to all antibiotic agents in all antibiotic classes identified.[13] See the Appendix (Tables A-1 and A-2) for resistance definitions and a list of antibiotics included in each antimicrobial category.

Klebsiella spp. isolates were also analyzed for possible extensive drug resistance (PXDR) and possible pandrug resistance (PPDR). Due to testing practices and data reporting practices, records may not fulfill XDR or PDR definitions referenced; however records may include sufficient data to reasonably suspect possible extensive or pandrug resistance. PXDR and PPDR definitions are based on the agents available for analysis and should be recognized as extensively resistant indicators.[13] See the Appendix (Tables A-3) for examples of possible antimicrobial susceptibility patterns. All PPDR isolates were checked against all available electronic medical records to confirm no additional susceptibility results were available.

Carbapenem resistance, defined as antibiotic non-susceptible to at least one carbapenem and resistant to all third generation cephalosporins tested, was also evaluated.[14]

Data Collection, Processing, and Analysis

The EDC utilized the World Health Organization's (WHO) BacLink and WHONET software applications to organize antibiotic susceptibilities within microbiology records. Surveillance cultures, defined as specimens isolated from nares, axilla, groin, and rectal swab samples, were excluded from consideration in this analysis, as surveillance cultures are typically indicative of colonization and not true infection. *Klebsiella* infections were counted on a rolling 30-day interval as a unique case for analysis to estimate annual prevalence of *Klebsiella*. The first *Klebsiella* infection per person, per year was used to identify the incidence of *Klebsiella*

infections and calculate annual incidence rates. Baseline rates, used to compare current observations to historical data, were calculated by taking the mean prevalence/incidence from 2007-2013. Demographic and clinical information for the specimen were described using the information within the HL7 formatted microbiology record. Microbiology data were used to identify beneficiary service of the sponsor (Air Force, Army, Marine Corps, or Navy), setting of specimen collection (inpatient or outpatient), gender, and beneficiary status (active duty, family member, retired, or other). *Klebsiella* infections were classified as UTIs (urinary tract and urine samples), BSIs (blood and blood vessel samples), or respiratory infections (respiratory discharge and respiratory tract samples); all remaining specimen sources and body sites were grouped as other.

To establish active duty status at the time of infection among DON cases, the microbiology cases were matched to the Defense Manpower Data Center (DMDC) personnel roster using a unique identifier. DON deployment-related cases were identified where the microbiology specimen collection dates occurred between the start and end dates of deployment in the DMDC Contingency Tracking System (CTS) database. The purpose of DMDC CTS is to capture personnel information for Central Command (CENTCOM) deployments, however locations beyond CENTCOM are included within the data. Including all locations in CTS allows for reporting of emerging infections among the locations present within the CTS data.

DON recruits were also identified using the DMDC active duty roster when the start of federal service date occurred during CY 2014. This analysis estimates the end of recruit training for each service member by calculating the date for the end of the standard training period from the start of federal service date (9 weeks for Navy recruit training and 13 weeks for Marine recruit training). If a microbiology record was identified for a recruit between the start date of federal service and seven days after the estimated end date of basic training, then the service member was considered a recruit case. All recruit cases were included in the active duty population.

To evaluate all laboratory-confirmed *Klebsiella* cases for recent healthcare exposure, *Klebsiella* cases were matched to SIDR records. Healthcare-associated (HA) cases were defined as patients who were currently hospitalized or had a hospitalization within the previous year. Current hospitalizations were then categorized as a hospital-onset (HO) case or a community-onset (CO) case. HO cases were defined as patients with a *Klebsiella* organism identified after the third day of the current admission. Community-onset (CO) cases were patients with a specimen collected within the first three days of the current admission yielding a *Klebsiella* organism, indicating the patient acquired the organism within the community and likely arrived at the treating facility with it.[12] Table 1 presents the definitions for healthcare exposure. Isolates not identified as an HA, were not included in healthcare exposure analysis.

Table 1. Healthcare Exposure Defintions[12]

Exposure	Definition
Healthcare-associated (HA)	Any case with a current hospitalization (specimen collection date date falls within admission and discharge date) or a previous hospitalization within the prior 12 months.
Previous hospitalization	Specimen collection date is not associated with a current admission (specimen collection date does not fall within an admission and discharge date) and the patient has a hospitalization within the previous 12 months.
Current hospitalization	Specimen collection date falls between a current admission and discharge date.
Hospital-onset (HO)	Specimen collection date is after the third day of admission.
Community-onset (CO)	Specimen collection date is within the first three days of admission.

[12] Cohen A, et al. Recommendations for metrics for multidrug-resistant organisms in healthcare settings: SHEA/HICPAC position paper. *Infection Control and Hospital Epidemiology*. 2008;29(10):901-913.
[a] Reason for hospitalization was not assessed and hospitalization could be due to any reason, including hospitalizations not indicating an infection.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 16 November 2015.

Established metrics were used to assess HAI exposure and infection burden for MDR *Klebsiella* organisms at DOD MTFs. HAI exposure burden metrics evaluate the admission prevalence and overall prevalence of MDROs within the healthcare facility. Admission prevalence measures the magnitude of importation of MDR *Klebsiella* into fixed MTFs. Overall prevalence measures the magnitude of a patient's exposure in the healthcare setting to other patients with the specific MDR organism. Though excluded from the general analysis, surveillance cultures were included in the overall and admission prevalence analysis, as they contribute to the colonization pressure and exposure burden for those not already colonized or infected. HAI infection burden metrics include HO bacteremia, HO UTIs, SSIs, central line-associated bloodstream infections (CLABSIs), and ventilator-associated pneumonia (VAP). All five metrics measure the burden of infections associated with and/or are a direct result of hospitalization. Infection burden metrics include the first HO MDR *Klebsiella* isolate per patient per admission. Device- and procedure-associated metrics (CLABSI, VAP, and SSI) require the use of International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) procedure codes in SIDR to identify the use of a device or performance of a procedure. Table 2 presents the classification for each metric.

Table 2. Classification of Healthcare-Associated Infection Metrics[12]

	Metric	Definition
Exposure Burden	Overall Prevalence	Any record where an MDR *Klebsiella* spp. was isolated from a specimen collected at any time during admission.
	Admission Prevalence	Any record where an MDR *Klebsiella* spp.was isolated from specimen collected within the first three days of admission.
Infection Burden	HO Bacteremia	Any record with body site or specimen source of blood that was collected at least three days after admission.
	HO UTI	Any record with body site or specimen source of urine that was collected at least three days after admission.
	SSI	Any record following the National Healthcare Safety Network (NHSN) operative procedure groupings;[15] The procedure is within admission and discharge dates; AND Infection occurs within 30 days of the procedure.
	CLABSI	Any record with body site or specimen source of blood; Records with ICD-9-CM procedure codes: 38.91, 38.92, 38.93, or 38.97; AND Specimen was collected at least three days after admission.
	VAP	Any record with body site or specimen source of respiratory sample; Records with ICD-9-CM procedure codes: 96.7, 96.04, 96.71, or 96.72; AND Specimen was collected at least three days after admission.

[12] Cohen A, et al. Recommendations for metrics for multidrug-resistant organisms in healthcare settings: SHEA/HICPAC position paper. *Infection Control and Hospital Epidemiology*. 2008;29(10):901-913.
[15] Centers for Disease Control and Prevention. Surgical site infections (SSI) event. CDC/NHSN Protocol and Instructions. http://www.cdc.gov/nhsn/PDFs/pscManual/9pscSSIcurrent.pdf?agree=yes&next=Accept. Published January 2013. Accessed January 2013.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 29 October 2015.

An antibiogram was developed for *Klebsiella* and MDR *Klebsiella* identified in 2014 using antibiotic susceptibility testing results within the HL7 formatted microbiology record according to the Clinical and Laboratory Standards Institute (CLSI) guidelines, which include the first isolate per person per year.[16] Antibiotics for the antibiogram were selected based on CLSI guidelines and frequency of testing in the MHS. Antibiotics were only reported if the antibiotic was tested ≥30 times. Nitrofurantoin and cephalothin required that specimens be from urine to reflect the clinical indications for which they would be considered.[17,18] Specimens for cefazolin susceptibility testing were categorized as urine or non-urine specimens, to provide susceptibility trends for the clinical indications for which the drug would be applicable.

To evaluate trends, historical antibiotic susceptibility data were included in the antibiogram from 2005-2014. Significance of the trends in susceptibility of relevant antibiotics was measured using the Cochran-Armitage trend test for linearity. Any antibiotic that showed a *p*-value of less than or equal to 0.05 was considered to have a significant trend.

HL7 formatted pharmacy records were used to identify antibiotic prescriptions associated with *Klebsiella* cases. HL7 formatted pharmacy data consist of three distinct databases depending on the patient setting where a provider prescribed the antibiotic and the route by which the antibiotic

was administered: outpatient oral antibiotics (OP), inpatient oral antibiotics (unit dose – UD), or intravenous (IV) antibiotics. For this analysis, prescriptions associated with a *Klebsiella* bacterium were identified as those with a pharmacy transaction date up to seven days following the microbiology specimen collection date, had a quantity dispensed greater than zero, and was not a cancelled record.

To provide a spatial context to *Klebsiella* cases in the DON and DOD in 2014, cases were grouped by TRICARE region. This was accomplished by using the Defense Medical Information System (DMIS) identification (ID) number of the facility requesting the microbiology test. Each facility is assigned a unique DMIS ID which is grouped into a TRICARE region.

Annual incidence and prevalence rates were calculated using MHS Data Mart (M2) beneficiary counts to obtain the number of TRICARE eligible beneficiaries by demographic category. Beneficiary counts were retrieved on a monthly basis for the monthly rate denominators. To provide context for 2014 annual incidence rates, the EDC calculated historic baseline incidence rates from 2007-2013 for eligible DOD beneficiaries and DON active duty service members.

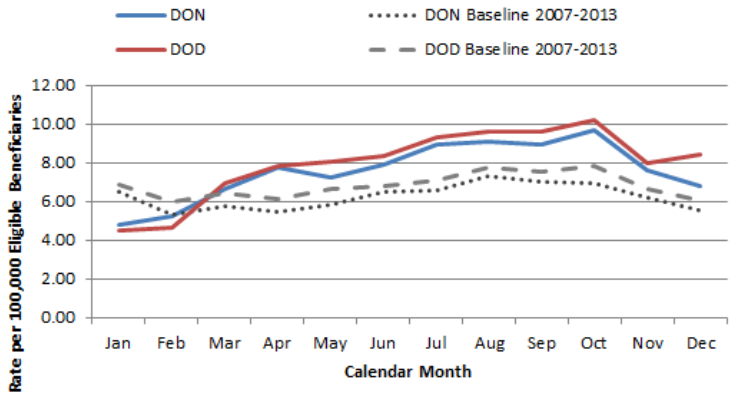
Results

Klebsiella Species Infections

DON/DOD

In 2014, the prevalence rate of *Klebsiella* spp. infections was below the baseline rates established for 2007-2013; however, from March through the remainder of the year, the rate of cases per 100,000 eligible beneficiaries remained above the baseline. In 2014, DON and DOD rates followed a general increasing trend until October, when rates began to decrease. *Klebsiella* has lacked a seasonal trend. October had the highest rate of cases for both the DON and DOD with the DOD rate approximately 30% higher than the baseline historic baseline rate (Figure 1). Each month from March on, had at least 55% more cases than the first two months of the year.

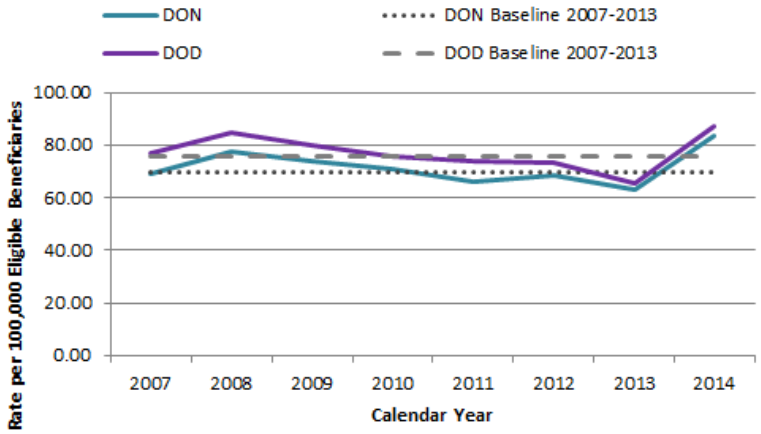
Figure 1. *Klebsiella* Species Infection Monthly Case Distribution in DON and DOD Beneficiaries with Monthly Baseline, 2014



Baseline calculated for all DON and DOD cases per 100,000 eligible beneficiaries from 2007-2013.
Data Source: NMCPHC HL7 formatted microbiology and M2 databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 January 2016.

Figure 2 displays the DON and DOD annual incidence for *Klebsiella* spp. compared to baseline rates. The overall incidence of *Klebsiella* cases from 2007-2013 showed a generally descending trend, however a 33% increase was observed from 2013 to 2014. In 2014, the DON was approximately 20% above baseline and the DOD was approximately 15% above baseline.

Figure 2. *Klebsiella* Species Infection Annual Incident Rate in DON and DOD Beneficiaries with Baseline, 2014



Baseline calculated for all DON and DOD cases per 100,000 eligible beneficiaries from 2007-2013.
Data Source: NMCPHC HL7 formatted microbiology and M2 databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 January 2016.

Table 3 presents the demographic rates for *Klebsiella* spp. infections within the DON and DOD beneficiary populations. In both populations, females were disproportionately affected and had approximately three and a half times the rate of infection as males. The rates were lowest among all beneficiaries less than 18 years of age. Rates were similar across all the services. When compared by beneficiary type, family members had the highest rates in both the DON and DOD, followed by active duty service members.

Table 3. Demographics of *Klebsiella* Species Infections in the DON and DOD, CY 2014

DON			DOD		
N=2,335	Count	Rate[a]	N = 8,047	Count	Rate[a]
Gender			**Gender**		
Female	1,898	141.2	Female	6,591	144.4
Male	437	30.0	Male	1,456	30.9
Age Group			**Age Group**		
0-17 years	165	29.4	0-17 years	576	29.7
18-24 years	484	112.8	18-24 years	1,217	104.3
25-34 years	344	96.1	25-34 years	1,190	100.8
35-44 years	215	88.8	35-44 years	854	105.9
45-64 years	580	93.5	45-64 years	2,064	100.5
65+ years	547	92.9	65+ years	2,146	101.0
Sponsor Service			**Sponsor Service**		
			Air Force	2,285	87.9
			Army	3,427	88.5
Marine Corps	643	86.2	Marine Corps	643	86.2
Navy	1,692	82.4	Navy	1,692	82.4
Beneficiary Type			**Beneficiary Type**		
Active duty	422	81.4	Active duty	1,128	82.2
Family member	1,606	104.6	Family member	5,687	115.5
Retired	270	43.3	Retired	1,054	50.3
Other	37	30.2	Other	178	20.3
TRICARE Region			**TRICARE Region**		
North	723	70.0	North	2,140	72.4
OCONUS	160	158.3	OCONUS	454	121.4
South	434	63.2	South	2,634	90.2
West	1,017	110.8	West	2,816	101.8
Unknown[b]	1		Unknown[b]	3	

*Rates for counts of <5 are not statistically relevant and are therefore not reportable.

[a] Rates per 100,000 eligible beneficiaries.

[b] TRICARE service region cannot be identified from the microbiology record.

Data Source: NMCPHC HL7 formatted microbiology and M2 databases.

Prepared by the EpiData Center, Navy and Marine Corps Public Health Center, on 21 January 2016.

Table 4 displays the clinical characteristics of *Klebsiella* cases in the DON and DOD. Most cases were identified in the outpatient setting and were predominantly from urinary tract specimens. Approximately 30% of infections in both the DON and DOD were healthcare-associated. The majority of cases were non-MDR infections (96.1%). The two PPDR cases within the DOD were both over 64 years of age and identified in urine specimens. Three CRE cases were also identified; all were female, over the age of 45, and identified in urine specimens.

Table 4. Clinical Description of *Klebsiella* Species Infections in the DON and DOD, CY 2014

DON				DOD			
N = 2,580		**Count**	**Percent**	**N = 8,894**		**Count**	**Percent**
Specimen Collection Location[a]				**Specimen Collection Location**[a]			
Inpatient		201	7.8%	Inpatient		648	7.3%
Outpatient		2,379	92.2%	Outpatient		8,246	92.7%
Healthcare Exposure				**Healthcare Exposure**			
Healthcare-associated(HA)[b]		772	29.9%	Healthcare-associated(HA)[b]		2,479	27.9%
HA-previous hospitalization		395 (51.0%)		HA-previous hospitalization		1,336 (53.8%)	
HA-current hospitalization	Hospital-onset[c]	72 (9.4%)		HA-current hospitalization	Hospital-onset[c]	212 (8.6%)	
	Community-onset[d]	305 (39.6%)			Community-onset[d]	931 (37.6%)	
Infection Type				**Infection Type**			
Urinary Tract		2,209	85.6%	Urinary Tract		7,797	87.7%
Blood Stream		43	1.7%	Blood Stream		134	1.5%
Respiratory		57	2.2%	Respiratory		176	2.0%
Wound		57	2.2%	Wound		271	3.0%
Other		214	8.3%	Other		516	5.8%
Species				**Species**			
Klebsiella pneumoniae		2,145	83.1%	*Klebsiella pneumoniae*		7,801	87.7%
Klebsiella oxytoca		259	10.0%	*Klebsiella oxytoca*		814	9.2%
Klebsiella ozaenae		16	0.6%	*Klebsiella ozaenae*		69	0.8%
Klebsiella species		161	6.2%	*Klebsiella* species		210	2.4%
Antibiotic Resistance Classification				**Antibiotic Resistance Classification**			
Klebsiella species		2,492	96.6%	*Klebsiella* species		8,549	96.1%
MDR *Klebsiella* species		59	2.3%	MDR *Klebsiella* species		262	2.9%
XDR *Klebsiella* species		0	0.0%	XDR *Klebsiella* species		0	0.0%
PDR *Klebsiella* species		0	0.0%	PDR *Klebsiella* species		0	0.0%
Possible XDR *Klebsiella* species		29	1.1%	Possible XDR *Klebsiella* species		80	0.9%
Possible PDR *Klebsiella* species		0	0.0%	Possible PDR *Klebsiella* species		2	0.0%
Carbapenem Resistant Enterobacteriaceae				**Carbapenem Resistant Enterobacteriaceae**			
Klebsiella species		1	0.0%	*Klebsiella* species		3	0.0%

[a] Based on MEPRS code within HL7 formatted microbiology data.
[b] Any isolate with an associated inpatient encounter record within the previous year. Denominator is total cases.
[c] Any inpatient isolate that has a specimen collection date after the third day of admission. Denominator is healthcare-associated infections.
[d] Any inpatient isolate that has a specimen collection date within the first three days of admission. Denominator is healthcare-associated infections.
Data Source: NMCPHC HL7 formatted microbiology and SIDR databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 January 2016.

During 2014 in the DOD, *Klebsiella* spp. were highly susceptible to many commonly prescribed antibiotics (Table 5). *Klebsiella* spp. were most susceptible to carbapenems (>99%), amikacin (99.8%), and cefotaxime (99.1%); nitrofurantoin had the lowest susceptibility (38.1%). Nitrofurantoin and cephalothin were the only significant trends increasing in resistance. All antibiotics, regardless of trend, with susceptibility over 85% were viable treatment options in 2014.

The *Klebsiella* spp. antibiogram for the DON population in 2014 had susceptibility results similar to the DOD, however there were several differences (data not shown). Cefazolin for non-urine isolates, cefotaxime, cephalothin (urine), and ciprofloxacin did not have significant trends (P=0.76, P=0.37, P=0.49, P=0.79, respectively). Cefoxitin, cefuroxime, and ertapenem (2008-2014) all had significant trends (P=0.02, P=0.05, P=0.03, respectively).All antibiotics were increasing in susceptibility except nitrofurantoin. Nitrofurantoin was also the only agent with a percent susceptible below 85%.

Table 5. Cumulative Annual Antibiogram of *Klebsiella* Species in the DOD with Trend Over Time, 2005-2014[a]

	Year											
Antibiotic	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	*P*-value[b]	Comment[d]
Amikacin	98.7%	98.1%	99.1%	99.4%	99.5%	99.6%	99.7%	99.5%	99.6%	99.8%	<.001	>
Amoxicillin/ Clavulanic Acid	95.3%	96.1%	95.3%	95.5%	95.4%	96.4%	96.3%	96.3%	96.7%	96.0%	0.01	>
Ampicillin/ Sulbactam	83.3%	85.9%	87.7%	89.6%	88.2%	87.0%	88.1%	88.8%	87.2%	85.9%	0.003	>
Aztreonam	94.3%	94.9%	95.2%	97.0%	97.1%	94.3%	96.1%	95.2%	95.5%	97.1%	0.004	>
Cefazolin (non-urine)^	81.1%	83.6%	85.2%	87.3%	87.8%	85.7%	85.8%	88.0%	85.6%	86.6%	<.001	>
Cefazolin (urine)^	95.2%	95.1%	95.7%	94.7%	95.4%	94.5%	94.4%	94.7%	93.8%	93.2%	0.13	
Cefepime	95.7%	96.0%	97.0%	97.9%	98.5%	98.3%	98.4%	98.6%	98.6%	98.0%	<.001	>
Cefotaxime	95.7%	97.3%	96.2%	97.9%	98.1%	99.0%	99.4%	98.2%	98.2%	99.1%	<.001	>
Cefoxitin	96.1%	96.0%	95.3%	93.6%	95.1%	96.2%	96.9%	96.5%	96.2%	96.5%	0.06	
Ceftazidime	95.8%	97.1%	97.4%	97.8%	98.4%	98.5%	98.0%	98.5%	98.5%	98.4%	<.001	>
Ceftriaxone	96.6%	96.9%	97.4%	98.0%	98.1%	97.3%	97.8%	98.4%	98.3%	97.8%	<.001	>
Cefuroxime	94.4%	94.9%	95.2%	96.4%	95.9%	96.0%	98.8%	94.3%	94.9%	94.6%	0.87	
Cephalothin (urine)^	90.2%	91.5%	89.5%	92.0%	89.0%	91.6%	91.2%	90.5%	90.8%	86.9%	<.001	<
Ciprofloxacin	96.4%	97.6%	97.5%	97.5%	97.4%	97.3%	97.3%	97.7%	97.9%	97.9%	<.001	>
Gentamicin	97.0%	97.5%	97.7%	98.6%	98.4%	98.4%	98.8%	98.9%	98.7%	98.6%	<.001	>
Ertapenem[c]	.	.	100.0%	99.9%	99.3%	99.6%	99.7%	99.9%	99.3%	99.8%	0.78	
Imipenem	99.9%	99.9%	99.8%	99.8%	99.8%	99.8%	99.5%	99.8%	99.4%	99.8%	0.20	
Levofloxacin	97.1%	98.0%	98.1%	98.0%	98.4%	98.4%	98.4%	98.4%	98.1%	98.6%	<.001	>
Meropenem	99.8%	99.6%	99.8%	100.0%	99.5%	99.7%	99.9%	99.6%	99.9%	99.9%	0.61	
Nitrofurantoin (urine)^	61.4%	58.6%	52.0%	48.0%	44.9%	44.1%	41.9%	38.0%	37.5%	38.1%	<.001	<
Piperacillin/ Tazobactam	95.1%	97.2%	98.1%	97.9%	97.4%	95.4%	97.3%	96.8%	96.9%	96.4%	0.59	
Tetracycline	88.5%	87.9%	90.2%	89.4%	89.2%	89.9%	88.7%	87.4%	89.1%	88.4%	0.76	
Tobramycin	95.4%	96.5%	97.3%	98.1%	98.4%	97.9%	97.9%	98.2%	98.4%	98.0%	<.001	>
Trimethoprim/Sulfamethoxazole	92.8%	93.9%	93.8%	93.8%	93.6%	93.0%	93.1%	93.7%	93.3%	93.4%	0.82	

[a] Antibiotics represent only those relevant antibiotics against which ≥30 isolates were tested.
[b] Trend and corresponding P-value were established for a single antibiotic over time using a two-tailed Cochrane-Armitage trend test for linearity.
[c] Cochrane-Armitage trend test 2007-2014.
[d] Direction of trend for significant Cochrane-Armitage trend tests.
^ Specimen sources limited by CLSI recommendations.
Data Source: NMCPHC HL7 formatted microbiology database.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 January 2016.

In 2014, the most common class of antibiotic prescribed for *Klebsiella* infections in the DOD was fluoroquinolones (39%). The fluoroquinolone most often administered was ciprofloxacin (65%), and it was primarily administered orally (n=95%, data not shown). Other commonly prescribed oral prescriptions were nitrofurantoin (17%) and trimethoprim/sulfamethoxazole (17%) (Table 6). By intravenous route, cephalosporins were the most frequently prescribed class (31%), however piperacillin/tazobactam (23%, data not shown) was the most frequent intravenous antibiotic prescribed followed by ceftriaxone (16%, data not shown). Other commonly prescribed intravenous antibiotics were levofloxacin (13%, data not shown) and ciprofloxacin (9%, data not shown). The DON 2014 prescriptions followed the same patterns (data not shown).

Table 6. Antibiotic Prescriptions for *Klebsiella* Species Infections in the DOD, CY 2014

Class	Oral (N=7,191)		Intravenous (N=1,099)		Antibiotic most frequently prescribed in class (overall)	Within Class	
	Count	Percent	Count	Percent	Antibiotic Name	Count	Percent
Aminoglycosides	5	0.1	68	6.2	Gentamicin	63	86.3
Cephalosporins	712	9.9	347	31.6	Ceftriaxone	288	27.2
Carbapenems	33	0.5	115	10.5	Meropenem	77	52.0
Fluoroquinolones	3,021	42.0	261	23.7	Ciprofloxacin	2,150	65.5
Fosfomycins	42	0.6	0	0.0	Fosfomycin*	42	100.0
Glycylcyclines	0	0.0	1	0.1	Tigecycline*	1	100.0
Monobactams	0	0.0	17	1.5	Aztreonam*	17	100.0
Nitrofurans	1,483	20.6	0	0.0	Nitrofurantoin*	1,483	100.0
Penicillins & Inhibitors	330	4.6	278	25.3	Piperacillin/Tazobactam	338	55.6
Polymyxins	1	0.0	0	0.0	Polymyxin B*	1	100.0
Pyramidines	8	0.1	0	0.0	Trimethoprim*	8	100.0
Rifamycins	14	0.2	0	0.0	Rifampin	11	78.6
Sulfonamides	1,441	20.0	4	0.4	Trimethoprim/Sulphmethoxazole*	1,445	100.0
Tetracyclines	101	1.4	8	0.7	Doxycycline	95	87.2

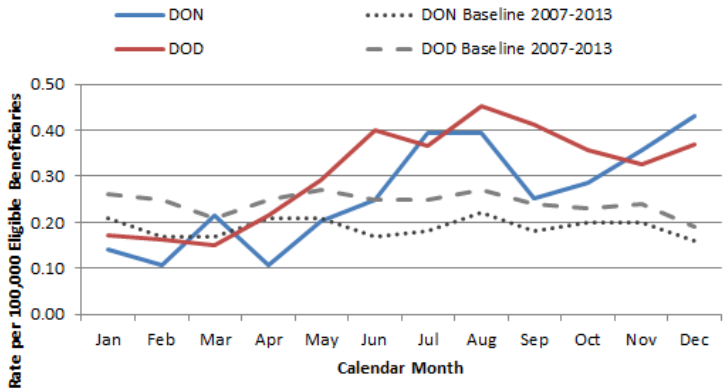
N=Total number of antibiotics prescribed of that type (oral or intravenous).
*Only antibiotic in class prescribed.
Data Source: NMCPHC HL7 formatted pharmacy database.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 January 2016.

MDR *Klebsiella* Species

DON/DOD

The monthly distributions of MDR *Klebsiella* spp. infections were below the DOD baseline rates established for 2007-2013 throughout the first quarter of 2014 for both the DON and DOD beneficiary populations. However, the DOD population exceeded the baseline in April and continued above the baseline through the remainder of the year. The DON population exceeed the baseline in March and May, and then remained above the DON baseline. Despite DON fluctuations, rates continued to increase and the year ended with the highest rate observed to date. Although the baselines lacked a seasonal trend, 2014 MDR *Klebsiella* cases peaked in summer months and again in December. During August the highest rate was observed for e DOD, with the 2014 rate over 100% higher than the historic baseline rate (Figure 3).

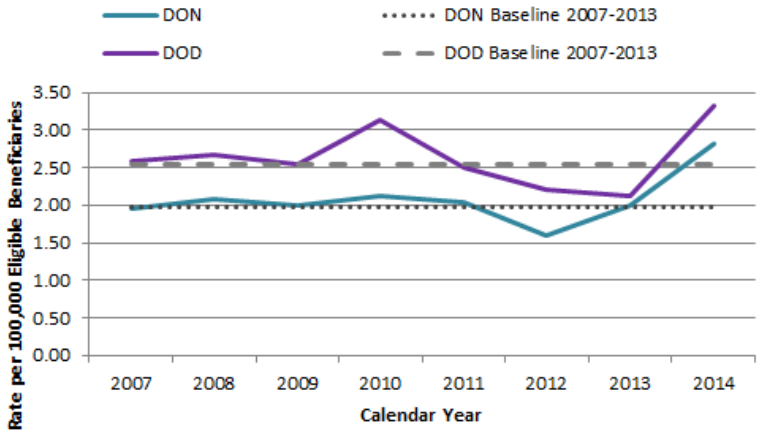
Figure 3. Multidrug-Resistant *Klebsiella* Species Infection Monthly Case Distribution in DON and DOD Beneficiaries with Monthly Baseline, 2014



Data Source: NMCPHC HL7 formatted microbiology and M2 databases.
Baseline calculated for all DON and DOD cases per 100,000 eligible beneficiaries from 2007-2013.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 January 2016.

Figure 4 displays the DON and DOD annual incidence for MDR *Klebsiella*. The 2014 incidence of DON and DOD MDR *Klebsiella* cases exceeded the historical baseline rate. In 2014, the DON was approximately 43% above the historical MDR baseline while the DOD was approximately 31% above.

Figure 4. Multidrug-Resistant *Klebsiella* Species Infection Annual Incident Rate in DON and DOD Beneficiaries with Baseline, 2014



Data Source: NMCPHC HL7 formatted microbiology and M2 databases.
Baseline calculated for all DON and DOD cases per 100,000 eligible beneficiaries from 2007-2013.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 January 2016.

Table 7 presents the rates by demographic factors for MDR *Klebsiella* within the DON and DOD. In both the DON and DOD, females were disproportionately affected and had approximately two times the infection rate of males. The rates were highest in all beneficiaries 65 years of age and older in both the DON and the DOD. In the DOD, rates were highest among Army and family member beneficiaries, and in the DON the rate was highest among retired beneficiaries.

Table 7. Demographics of Multidrug-Resistant *Klebsiella* Species Infections in the DON and DOD, CY 2014

DON			DOD		
N = 79	Count	Rate[a]	N = 308	Count	Rate[a]
Gender			**Gender**		
Female	52	3.9	Female	199	4.4
Male	27	1.9	Male	109	2.3
Age Group			**Age Group**		
0-17 years	3	--	0-17 years	18	0.9
18-24 years	8	1.9	18-24 years	24	2.1
25-34 years	3	--	25-34 years	33	2.8
35-44 years	9	3.7	35-44 years	29	3.6
45-64 years	19	3.1	45-64 years	91	4.4
65+ years	37	6.3	65+ years	113	5.3
Sponsor Service			**Sponsor Service**		
			Air Force	76	2.9
			Army	153	4.0
Marine Corps	15	2.0	Marine Corps	15	2.0
Navy	64	3.1	Navy	64	3.1
Beneficiary Type			**Beneficiary Type**		
Active duty	8	1.5	Active duty	30	2.2
Family member	48	3.1	Family member	186	3.8
Retired	20	3.2	Retired	78	3.7
Other	3	--	Other	14	1.6
TRICARE Region			**TRICARE Region**		
North	17	1.6	North	91	3.1
OCONUS	10	9.9	OCONUS	20	5.3
South	13	1.9	South	114	3.9
West	39	4.3	West	82	3.0
Unknown[b]	0		Unknown[b]	1	

*Rates for counts of <5 are not statistically relevant and are there for not reportable.

[a] Rates per 100,000 eligible beneficiaries.

[b] TRICARE service region cannot be identified from the microbiology record.

Data Source: HL7 microbiology and M2 databases.

Prepared by the EpiData Center, Navy and Marine Corps Public Health Center, on 21 January 2016.

Table 8 displays the clinical characteristics of MDR *Klebsiella* cases in the DON and DOD. Most cases were identified in the outpatient setting and were predominantly from urinary tract specimens. Healthcare-associated cases made up a larger proportion of MDR infections (45.0%) than in *Klebsiella* infections overall (27.7%).

Table 8. Clinical Description of Multidrug-Resistant *Klebsiella* Species Infections in the DON and DOD, CY 2014

DON				DOD			
N = 89		**Count**	**Percent**	**N = 345**		**Count**	**Percent**
Specimen Collection Location[a]				**Specimen Collection Location**[a]			
Inpatient		15	16.9%	Inpatient		49	14.2%
Outpatient		73	82.0%	Outpatient		296	85.8%
Healthcare Exposure				**Healthcare Exposure**			
Healthcare-associated(HA)[b]		50	56.2%	Healthcare-associated(HA)[b]		156	45.2%
HA-previous hospitalization		20 (40.8%)		HA-previous hospitalization		70 (45.1%)	
HA-current hospitalization	Hospital-onset[c]	9 (18.4%)		HA-current hospitalization	Hospital-onset[c]	22 (14.4%)	
	Community-onset[d]	21 (40.8%)			Community-onset[d]	64 (40.5%)	
Infection Type				**Infection Type**			
Urinary Tract		77	86.5%	Urinary Tract		306	88.7%
Blood Stream		1	1.1%	Blood Stream		5	1.4%
Respiratory		5	5.6%	Respiratory		15	4.3%
Wound		1	1.1%	Wound		7	2.0%
Other		5	5.6%	Other		12	3.5%
Species				**Species**			
Klebsiella pneumoniae		74	83.1%	*Klebsiella pneumoniae*		302	87.5%
Klebsiella oxytoca		9	10.1%	*Klebsiella oxytoca*		35	10.1%
Klebsiella ozaenae		3	3.4%	*Klebsiella ozaenae*		5	1.4%
Klebsiella species		3	3.4%	*Klebsiella* species		3	0.9%

[a] Based on MEPRS code within HL7 formatted microbiology data.
[b] Any isolate with an associated inpatient encounter record within the previous year. Denominator is total cases.
[c] Any inpatient isolate that has a specimen collection date after the third day of admission. Denominator is healthcare-associated infections.
[d] Any inpatient isolate that has a specimen collection date within the first three days of admission. Denominator is healthcare-associated infections.
Data Source: NMCPHC HL7 formatted microbiology and SIDR databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 January 2016.

Healthcare-associated infection metric rates for MDR *Klebsiella* are presented in Table 9. The rate of MDR *Klebsiella* present upon admission to DOD MTFs was 0.41 per 1,000 admissions in 2014. However, the overall prevalence of MDR *Klebsiella* was 0.51 per 1,000 admissions. In 2014, MDR *Klebsiella* was associated with CLABSIs at a rate of 0.04 per 1,000 central-line days, VAPs at a rate of 0.03 per 1,000 ventilation-days, and SSIs at a rate of 0.04 per 1,000 procedures at DOD MTFs. Rates for HO bacteremia and HO UTI were low.

Table 9. Healthcare-Associated Infection Metrics for Multidrug-Resistant *Klebsiella* Species Infections in DOD Beneficiaries, 2014

Metric	Rate/Density-Rate	
Exposure Burden		
Admission Prevalence	0.41	per 1,000 Admissions
Overall Prevalence	0.51	per 1,000 Admissions
Infection Burden		
HO Bacteremia	0.004	per 1,000 Patient-Days
HO UTI	0.01	per 1,000 Patient-Days
Device Associated		
CLABSI	0.04	per 1,000 Central-Line Days
VAP	0.03	per 1,000 Vent-Days
Procedure Associated		
SSI	0.04	Per 1,000 Procedures

Data Source: SIDR and HL7 formatted microbiology databases.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 January 2016.

In the DOD in 2014, MDR *Klebsiella* was highly susceptible to few (carbapenems (>95%) and amikacin (99.3%)) commonly prescribed antibiotics (Table 10). Ampicillin/sulbactam had the lowest susceptibility (6.1%), followed by cephalothin (14.0%, urine), tetracycline (19.3%), and nitrofurantoin (23.3%). Nitrofurantoin is the only agent with a decreasing trend. All antibiotics, regardless of trend, with susceptibility over 85% were viable treatment options in 2014. The DON had too few isolates to accurately display trends and susceptibility profiles over time (data not shown).

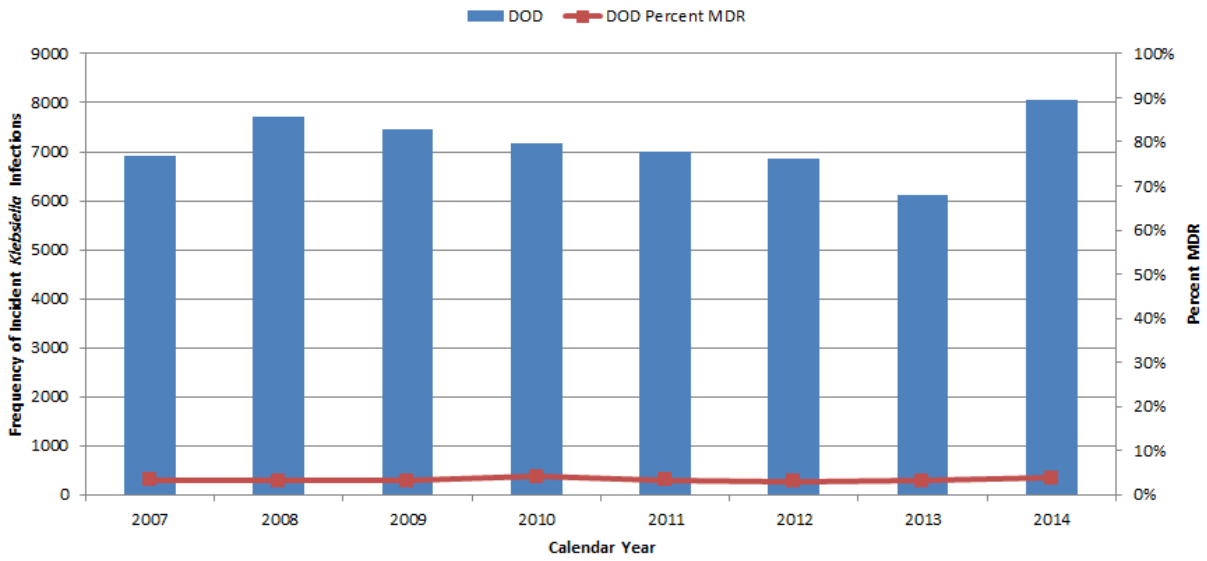
Table 10. Cumulative Annual Antibiogram of Multidrug-Resistant *Klebsiella* Species in the DOD with Trend Over Time, 2005-2014[a]

Antibiotic	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	*P*-value[b]	Comment[d]
Amikacin	87.6%	78.5%	85.9%	92.2%	91.3%	94.4%	96.0%	94.5%	94.3%	99.3%	<.001	>
Amoxicillin/ Clavulanic Acid	52.6%	48.0%	36.8%	25.4%	32.7%	54.2%	34.0%	45.3%	52.5%	49.4%	0.13	
Ampicillin/ Sulbactam	7.0%	6.2%	7.5%	5.3%	9.4%	6.3%	5.5%	7.4%	9.4%	6.1%	0.84	
Aztreonam	35.6%	25.2%	30.6%	42.6%	50.0%	41.2%	51.4%	60.2%	63.3%	57.5%	<.001	>
Cefazolin (non-urine)^	4.8%	6.7%	8.9%	16.7%	14.7%	15.3%	12.8%	17.6%	29.4%	26.7%	<.001	>
Cefazolin (urine)^	36.6%	27.9%	32.1%	26.7%	32.9%	32.8%	29.3%	37.9%	28.2%	26.1%	0.23	
Cefepime	40.0%	35.8%	48.4%	54.5%	68.4%	67.3%	62.4%	64.3%	66.0%	59.3%	<.001	>
Cefotaxime	36.0%	32.8%	37.9%	51.0%	66.1%	86.0%	91.4%	83.9%	80.0%	84.2%	<.001	>
Cefoxitin	47.7%	52.3%	56.3%	41.7%	43.5%	69.9%	62.7%	59.6%	40.9%	67.2%	0.07	
Ceftazidime	35.9%	38.0%	39.6%	51.9%	66.1%	73.5%	54.3%	69.0%	69.2%	64.4%	<.001	>
Ceftriaxone	44.4%	34.5%	41.1%	43.9%	55.9%	54.0%	49.1%	61.1%	60.4%	53.0%	<.001	>
Cefuroxime	30.3%	25.5%	27.8%	42.3%	38.5%	60.9%	50.0%	44.0%	44.6%	40.8%	<.001	>
Cephalothin (urine)[c,^]	20.8%	13.5%	16.2%	13.3%	.	57.1%	23.3%	18.8%	.	14.0%	0.53	
Ciprofloxacin	44.8%	44.4%	46.0%	45.0%	46.7%	57.4%	45.4%	53.6%	57.0%	62.6%	<.001	>
Gentamicin	40.9%	42.2%	44.4%	63.9%	64.9%	66.7%	68.9%	70.7%	69.9%	71.2%	<.001	>
Ertapenem[c]	.	.	.	97.4%	85.7%	93.8%	93.8%	98.4%	89.7%	98.3%	0.12	
Imipenem	98.4%	97.9%	96.9%	97.0%	96.4%	96.0%	94.1%	97.2%	93.6%	97.5%	0.09	
Levofloxacin	49.2%	48.2%	54.8%	52.6%	62.3%	68.8%	63.3%	70.9%	66.7%	79.4%	<.001	>
Meropenem	98.4%	95.5%	97.5%	100.0%	91.9%	96.8%	92.6%	88.5%	96.9%	97.7%	0.30	
Nitrofurantoin (urine)^	36.4%	37.8%	33.7%	33.1%	25.5%	29.1%	26.7%	22.8%	25.2%	23.3%	<.001	<
Piperacillin/ Tazobactam	43.2%	56.6%	63.0%	54.1%	56.2%	47.3%	58.6%	61.5%	53.6%	59.6%	0.03	>
Tetracycline	22.3%	15.3%	18.5%	16.5%	30.3%	44.5%	31.2%	19.5%	21.8%	19.3%	0.32	
Tobramycin	37.5%	34.9%	43.2%	61.6%	65.6%	62.4%	57.5%	63.1%	66.9%	67.0%	<.001	>
Trimethoprim/Sulfamethoxazole	23.6%	25.6%	26.5%	28.7%	34.3%	41.2%	34.5%	37.9%	37.4%	41.8%	<.001	>

[a] Antibiotics represent only those relevant antibiotics against which ≥30 isolates were tested.
[b] Trend and corresponding P-value were established for a single antibiotic over time using a two-tailed Cochrane-Armitage trend test for linearity.
[c] Cochrane-Armitage trend test performed on years with ≥30 isolates.
^ Specimen sources limited by CLSI recommendations
Data Source: NMCPHC HL7 formatted microbiology database.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 January 2016.

In 2014, 3.4% and 3.8% of incident infections were MDR infections in the DON and DOD, respectively (Figure 5). This was the highest percent of incident infections for the DON within the surveillance time period (data not shown). The DOD percent was highest in 2010, with 4.1% of incident infections identified as MDR. However, the percent of DOD MDR incident infections remains below 5%.

Figure 5. Frequency of *Klebsiella* Species Annual Incident Infections with percent Multidrug-Resistant *Klebsiella* Species Infections in DOD Beneficiaries, 2007-2014



Data Source: NMCPHC HL7 formatted microbiology.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 25 January 2016.

Klebsiella Species – Special Populations

DON Active Duty

During 2014, there were a total of 407 *Klebsiella* cases (annual incidence rate: 78.5 cases per 100,000) identified among DON active duty service members. The highest rates were among Navy service members, females, or those 18-24 years of age (Table 11).

Table 11. Demographics of *Klebsiella* Species Infections in Active Duty DON Service Members, CY 2014

N = 407	Count	Rate[a]
Gender		
Female	301	415.4
Male	106	45.7
Age Group		
18-24 years	248	106.9
25-34 years	109	57.0
35-44 years	41	52.2
45-64 years	9	56.0
Sponsor Service		
Marine Corps	125	65.7
Navy	282	86.0
TRICARE Region		
North	127	66.0
OCONUS	55	107.6
South	70	99.4
West	155	85.0

[a] Rates per 100,000 DON active duty service members.
Data Source: NMCPHC HL7 formatted microbiology and M2 databases.
Prepared by the EpiData Center, Navy and Marine Corps Public Health Center, on 21 January 2016.

Table 12 displays the clinical characteristics of DON active duty *Klebsiella* cases. Cases were most frequently identified in the outpatient setting (95.0%) and from urinary tract specimens (79.0%). The majority of the inpatient DON active duty cases had a CO exposure. This indicates that organism acquisition for these cases was most commonly associated with exposures outside of the MHS. There were eight (1.9%) MDR *Klebsiella* cases and no CRE cases identified in DON active duty service members in 2014.

Table 12. Clinical Description of *Klebsiella* Species Infections in Active Duty DON Service Members, CY 2014

N = 426		Count	Percent
Specimen Collection Location[a]			
Inpatient		22	5.2%
Outpatient		404	94.8%
Healthcare Exposure			
Healthcare-associated(HA)[b]		68	16.0%
HA-previous hospitalization		40 (56.1%)	
HA-current hospitalization	Hospital onset[c]	7 (10.6%)	
	Community onset[d]	21 (33.3%)	
Infection Type			
Urinary Tract		336	78.9%
Blood Stream		1	0.2%
Respiratory		3	0.7%
Wound		21	4.9%
Other		65	15.3%
Antibiotic Resistance Classification			
Klebsiella species		418	98.1%
MDR *Klebsiella* species		8	1.9%
XDR *Klebsiella* species		0	0.0%
PDR *Klebsiella* species		0	0.0%
Possible XDR *Klebsiella* species		0	0.0%
Possible PDR *Klebsiella* species		0	0.0%
Carbapenem Resistant Enterobacteriaceae			
Klebsiella species		0	0.0%

[a] Based on MEPRS code within HL7 formatted microbiology data.

[b] Any isolate with an associated inpatient encounter record within the previous year. Denominator is total cases.

[c] Any inpatient isolate that has a specimen collection date after the third day of admission. Denominator is healthcare-associated infections.

[d] Any inpatient isolate that has a specimen collection date within the first three days of admission. Denominator is healthcare-associated infections.

Data Source: NMCPHC HL7 formatted microbiology and SIDR databases.

Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 21 January 2016.

DON Deployed

DON service members deployed had a *Klebsiella* incidence infection rate of 4.9 per 100,000 deployed DON service members in 2014, this represents 10 individuals with 11 infections. Females had a higher proportion of infections (70%). The infections were evenly split between Bahrain and locations designated as afloat or unknown. The majority of infections occurred in among Navy service members (80%), and were 18-24 year olds (60%). Specimens were primarily collected in the outpatient setting (90.9%), were not healthcare-associated (90.9%), and were urinary tract specimens (63.6%). None of the infections were identified as a CRE or MDR infection.

DON Recruits

DON recruits had an overall incidence rate of 24.4 per 100,000 DON recruits per year for *Klebsiella* in 2014 (n=16). The highest rates of infection were among males (22.3 per 100,000) and Marine Corps recruits (44.8 per 100,000). Specimens were predominantly collected in the outpatient setting (93.8%) and were primarily from 'other' specimen sources (50%). No MDR or CRE cases were identified among DON recruits.

Discussion

For 2014, incident rates of *Klebsiella* and MDR *Klebsiella* infections were above historical baselines and exceeded historical peaks. In 2014 the increase reported was a shift from the gradually declining trend observed from 2008-2013. MDR infections accounted for 3.8% of *Klebsiella* incident infections in 2014. MDR *Klebsiella* infections have fluctuated in historical data, and were 43% above baseline. The increase seen in 2014 may have been impacted by better data capture from the Defense Health Service System (DHSS) implemented in March of 2014.

UTIs were the most common manifestation of *Klebsiella* bacteria and females were most impacted by *Klebsiella* UTIs. *Klebsiella* is not a rare causative agent of UTIs and studies report that *Klebsiella* spp. may account for 6-15% of inpatient and outpatient UTIs.[19,20] UTIs are more prevalent among women and research suggests that approximately half of all women will experience one UTI during their lifetime.[21]

Beneficiaries less than 17 years of age made up approximately one third of the incidence rate (29.4 cases per 100,000 eligible beneficiaries). Urology experts estimate that 3-8% of prepubertal girls and 1% of prepubertal boys are diagnosed with UTIs.[22] UTIs in children can cause long-term medical sequelae, therefore prompt diagnosis and management is important to prevent subsequent complications.

Females of reproductive age are frequently impacted by *Klebsiella* infections. Asymptomatic bacteriuria (ASB) is a condition where treatment is not generally recommended except during pregnancy to prevent complications; therefore women of reproductive age may be captured during pregnancy screening. The US Preventive Services Task Force and the Infectious Disease Society of America (IDSA) found no evidence for improved outcomes with UTI screenings in other populations, and therefore only recommend screening for ASB among pregnant women

and those undergoing urologic procedures.[23,24] Pregnancy screening likely did not affect the identification of *Klebsiella* among women of reproductive age, because approximately 4% of the *Klebsiella* cases had a pregnancy related diagnosis code (V22—Normal Pregnancy, V23—Supervision of High-Risk Pregnancy, 630-679—Complications of Pregnancy, Childbirth, and the Puerperium).

Although MDR *Klebsiella* infections occurred far less frequently than non-MDR *Klebsiella*, the rate was highest among beneficiaries 65 and older. Among geriatric populations, there are additional factors that make UTIs more difficult to diagnose and manage. Older populations generally have more comorbid conditions and potentially more urinary symptoms unrelated to disease or infection. Urology experts have reported that a broader spectrum of infecting organisms affects this population.[22] Within our data, approximately half of the MDR infections were healthcare-associated compared to approximately a third of non-MDR *Klebsiella* infections. This suggests that higher exposure to procedures and potential reservoirs for MDR infections among older beneficiaries.

Klebsiella infections among active duty DON service members followed trends similar to the overall trends observed among the general DON and DOD populations. Infections manifested mainly as UTIs among younger females with only a small proportion identified as MDR infections (2%). The percent of hospital-onset infections was slightly higher (10.6%) in active duty DON service members than the general DOD population (8.6%). Infections were infrequent among deployed DON service members. Despite the low frequencies and small proportion of MDR isolates, this is an important population for continued surveillance to maintain troop readiness.

Klebsiella isolates retained high susceptibilities to many tested antibiotics, indicating a range of viable treatment options for infections. Nitrofurantoin, a recommended agent for uncomplicated UTIs, was the least susceptible and decreased in susceptibility over the surveillance period. Although Johns Hopkins recommends nitrofurantoinfor uncomplicated UTIs caused by *Klebsiella*, however the relationship may need more investigating.[25] The European Committee on Antimicrobial Susceptibility (EUCAST), only provides breakpoints for *Escherichia coli* and the Food and Drug Administration (FDA), acknowledges some strains of *Klebsiella* species may be resistant.[26,27] Both indicating that more research is need to understand the relationship of *Klebsiella* and nitrofurantoin. The use of nitrofurantoin for *Klebsiella* infections should be assessed at the local level and resistance rates between 15-20% necessitate a change in antibiotic class.[28] Ciprofloxacin, nitrofurantoin, and trimethoprim/sulfamethoxazole, all of which are recommended for uncomplicated UTI treatment, were the most commonly prescribed antibiotics associated with *Klebsiella* infections.[29]

MDR *Klebsiella* infections had far fewer treatment options and were limited to mainly the carbapenems, a class of antibiotics that is already considered a last resort treatment. Despite the infrequent identification of CREs, resistant genotypes can confer resistance to additional antibiotic classes. Although they are only one class of resistance among *Klebsiella* organisms, carbapenamase producing CREs are associated with treatment failure and high mortality. Within

the literature, patients with CRE infections may have better outcomes if they are given combination therapy.[30] Patient reports and case studies have shown better outcomes with carbapenems and polymyxins as part of the combination, however the best combination has not been established.[30] To continue to ensure that viable treatments remain available for *Klebsiella* infections and to prevent *Klebsiella* organisms from increasing in resistance and/or passing resistant determinants to other organisms, it is advised that providers practice strict antimicrobial stewardship, prescribe treatment using individual organism resistance patterns as well as local antibiograms, and educate patients to prevent the propagation of these organisms and their progression to higher levels of resistance.

This annual report summarized *Klebsiella* spp. infection rates and characteristics in the DON and DOD beneficiary populations in 2014 and reported changes from previously identified trends. Given the association of *Klebsiella* with common types of infection, namely female UTIs, and the recent increase in common infections caused by resistant bacteria, it is important to monitor and manage the significant risk presented by MDR organisms in order to control the proliferation of resistance to other infection types. This is especially true for *Klebsiella* spp., which have the ability to transfer resistance to other bacteria within and outside their respective genus. Continued surveillance of *Klebsiella* is recommended.

Limitations

HL7 formatted data are generated within the CHCS at fixed MTFs. Microbiology testing results only list the organism(s) that were identified, not the intended tests (e.g., if a physician suspects an organism different from the one that was identified, the record will not show the organism that the physician suspected). Microbiology data are used to identify laboratory-confirmed cases of illness. However, the microbiology data does not capture cases in which a physician chose to treat presumptively without laboratory confirmation. Therefore, the isolate counts here are likely an underestimate of the actual burden of the *Klebsiella* spp. infections within the DOD. However, on the opposite side of the spectrum, microbiology data also does not capture if the specimen was collected for screening purposes. Screening of patients may inflate *Klebsiella* infection counts with organism identifications not clinically relevant. The assumption is made that all *Klebsiella* identifications were prompted by appropriate clinical symptoms.

The use of microbiology data for analysis of antibiotic resistance is limited by the practice of cascade reporting, where antibiotic sensitivity results are conditionally reported to CHCS to guide treatment decisions. DOD MTFs practice cascade reporting to varying degrees. Furthermore, not all laboratories in the DOD operate under the same recommendation guidelines. As a result, certain facilities use guidelines not aligned with the most current CLSI guidelines. Thus, the EDC cannot project a complete picture of the susceptibility patterns for *Klebsiella* and the presumption of reduced susceptibility is applied to all antibiotics in a class if an isolate is shown to be resistant to that class. This may have led to some misclassifications of the level of resistance. The 2014 update has incorporated PXDR and PPDR to adjust for cascade reporting, however this report may be an underestimate of true MDR and/or XDR burden in the DOD. Although PXDR and PPDR are recognized indicators of extensive resistance, and should be used despite the limitations, they are not comparable with other studies because characterization depends on which antimicrobial agents are tested and reported.[6]

Microbiology bacterial culture records are extracted and assessed for antibiotic resistance patterns using BacLink and WHONET. The data restructuring process does not capture non-standard CHCS records. These non-standard records may include those containing the results of tests performed at reference laboratories, novel organism antibiotic combinations, or test results not recorded in the standard microbiology format. Additionally, some results of rapid screening tests, such as plate or polymerase chain reaction (PCR) methods, are included in microbiology data, and are not consistently captured. Occasionally, facilities feed data in the non-standard format. One such facility had 144 *Klebsiella* isolates; however, resistance patterns were not able to be assessed due to the data structure, therefore possibly contributing to the underestimate of MDR infections.

A SIDR is created at discharge or transfer from an inpatient MTF for all TRICARE beneficiaries. Data for medical surveillance are considered provisional and medical case counts may change if the discharge record is edited after the patient is discharged from the MTF. As this report presents an annual summary and several months were allotted in the new year to account for possible data lag and record corrections, it can be presumed with relative certainty that the

records identified are the final and complete records for an inpatient encounter; however, the possibility does exist that records still may be modified, thereby altering the case counts. Ambulatory records are created at the close out of an outpatient medical encounter at DOD MTFs for all TRICARE beneficiaries.

Within the DMDC data, misclassification may occur due to the monthly snapshot structure of the data. The monthly snapshots provide each active duty, reserve, and deployed Navy and Marine Corps service members' personnel record. Any changes in service member status, for example deactivation, after the monthly snapshot data are extracted will not be captured until the following month. Active duty and reserve personnel records are maintained in separate databases. In this analysis only the active duty personnel records were assessed. Activated reservists may be captured in the active duty DMDC and not the reserve DMDC file. In this analysis it is unknown the impact of activated reservists not being captured in active duty database.

Misclassification of cases as deployment related is possible and could lead to over or under estimation of *Klebsiella* infection burden associated with deployment. Within CTS, deployment start and end dates are derived from different systems and may not reflect the actual dates of deployment. Additionally, the CTS database captures some locations outside of CENTCOM. This capture is not comprehensive for deployments that are not CENTCOM related, as such this data source does not provide a robust analysis of all deployment related events.

The pharmacy databases consist of outpatient non-intravenous prescriptions (Outpatient), inpatient non-intravenous prescriptions (Unit-Dose), and intravenous prescriptions (Intravenous). Though treatment compliance in the inpatient setting can be assumed, outpatient pharmacy records indicate that a patient received a prescription and subsequent compliance is unknown. Due to near real-time data feeds, analysts are able to determine if a prescription was edited or canceled; however, the time difference between these events may allow for a short period of treatment not considered in this analysis. Prescriptions with quantities dispensed of zero or cancelled records were not included in this analysis. During ongoing surveillance efforts, patient treatment status may change as edited or canceled prescription records are received. In addition, providers may not have prescribed the antibiotics in response to the *Klebsiella* bacteria identified in this report. It is possible that antibiotics dispensed around the same timeframe as the positive gram-negative culture reflect treatment for other reasons. As previously mentioned, cases where a physician chose to treat presumptively were not captured because HL7 formatted microbiology records were used to define cases.

All the above mentioned databases are limited in that they do not include data from purchased care providers, shipboard facilities, battalion aid stations, or in-theater facilities. Therefore, these results are only an estimate of the true *Klebsiella* bacterial burden in the DON and DOD. In addition, the proportion of cases imported from outside the treating MTF's geographic area is unknown.

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Appendix

Table A-1. EDC Antibiotic Resistance Definitions and Antibiotic Classes[a] Used for Classification of *Klebsiella* spp. in the DOD, CY 2014

	Aminoglycosides	Anti-MRSA cephalosporins	Antipseudomonal carbapenems	Antipseudomonal cephalosporins	Antipseudomonal fluroquinolones	Antipseudomonal penicillins+inhibitors	Carbapenems	Cephamycins	Extended Spectrum cephalosporins	Fluoroquinolones	Folate Pathway Inhibitors	Glycylcyclines	Monobactams	Non-extended spectrum cephalosporins	Penicillins	Penicillins+inhibitors	Phosphoric acids	Polymyxins	Tetracyclines
Klebsiella species[b,c]	x	x		x	x	x	x	x	x	x	x	x	x		x	x	x	x	
Carbapenem-Resistant Enterobacteriaceae	Non-susceptbile[d] to a carbapenem and resistant to all 3rd generation cephalosporins tested																		

[a] See Table A-2 for a list of antibiotics used in each class.

[b] MDR: Non-susceptible to ≥1 antibiotic in ≥3 of the marked classes.
XDR: Non-susceptible to ≥1 antibiotic in all but ≤2 of the marked classes.
PXDR: Non-susceptible to ≥1 antibiotic in all but ≤2 of the marked classes the isolate was tested against. An adjusted definition of XDR due to cascade reporting of results accounting for the antibiotics received within the data.
PDR: Non-susceptible to all antimicrobial agents in all marked classes.
PPDR: Non-susceptible to all antimicrobial agents in all marked classes the isolate was tested against. An adjusted definition of PDR due to cascade reporting of results accounting for the antibiotics received within the data.

[c] Anti-MRSA cephalosporins used only for *K. pneumonaie* and *K. oxytoca*.

[d] Non-susceptible: resistant or intermediately susceptible to a given antibiotic.

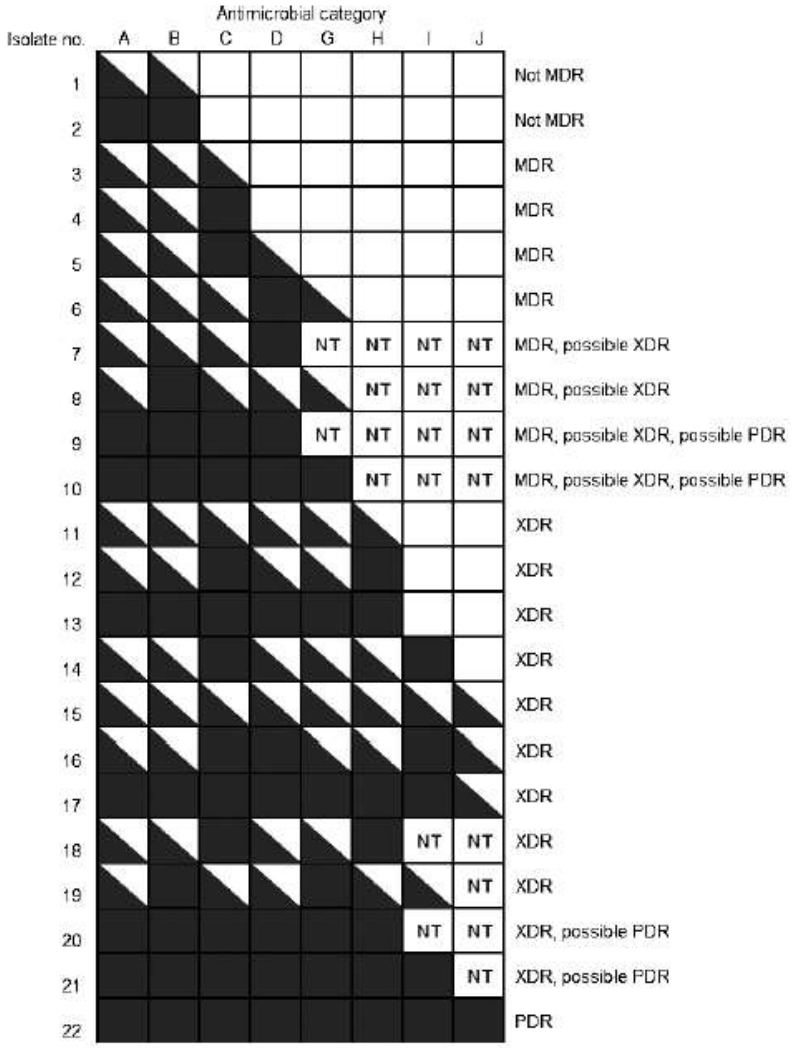
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 15 December 2015.

Table A-2. Antibiotics Included in the Resistance Definitions for *Klebsiella* spp. in the DOD, CY 2014

Antibiotic Class	Antibiotics Inlcuded in Class
Aminoglycosides	Amikacin
	Gentamicin
	Netilmicin
	Tobramycin
Anti-MRSA cephalosporins[a]	Ceftaroline
Antipseudomonal penicillins & β-lactamase inhibitors	Piperacillin/Tazobactam
	Ticarcillin/Clavulanic Acid
Carbapenems	Doripenem
	Ertapenem
	Imipenem
	Meropenem
1st & 2nd Generation Cephalosporins (non-extended specturm cephalosporins)	Cefazolin
	Cefuroxime
3rd & 4th Gneration Cephalosporins (Extended spectrum cephalosporins)	Cefotaxime or ceftriaxone
	Ceftazidime
	Cefepime
Cephamycins	Cefoxitin
	Cefotetan
Fluoroquinolones	Ciprofloxacin
	Levofloxacin[c]
Folate pathway inhibitors	Trimethoprim/Sulfamethoxazole
Glycylcyclines	Tigecycline
Monobactam	Aztreonam
Penicillins & β-lactamase inhibitors	Amoxicillin/Clavulanic Acid
	Ampicillin/Sulbactam
Phenicols	Chloramphenicol
Phosphoric Acid	Fosfomycin
Polymyxins	Colistin
Tetracyclines	Doxycycline
	Minocycline
	Tetracycline

[a] Included only for *Klebsiella pneumoniae* and *K. oxytoca*.
Source: Magiorakos et al., 2012.
Prepared by the EpiData Center Department, Navy and Marine Corps Public Health Center, on 02 October 2014.

Table A-3. Examples of 22 Possible Antimicrobial Susceptibility Patterns That Can Fall Under the Proposed Definitions for MDR, XDR, and PDR[13]



The isolate is susceptible to all agents listed in category.
The isolate is non-susceptible to some, but not all agents listed in category.
The isolate is non-susceptible to all agents listed in category.
NT The isolate was not tested for susceptibility to any agent listed in this category.

[13]Source: Magiorakos et al., 2012.

Acronym/Abbreviation List

Acronym/Abbreviation	Definition
AOR	Area of Responsibility
BSI	Blood stream infection
CAUTI	Catheter-associated urinary tract infection
CENTCOM	United States Central Command
CHCS	Composite Health Care System
CLABSI	Central-line associated blood stream infection
CLSI	Clinical and Laboratory Standards Institute
CO	Community-onset
CRE	Carbapenem-Resistant Enterobacteriaceae
CTS	Contingency Tracking System
CY	Calendar year
DHSS	Defense Health Surveillance System
DMDC	Defense Manpower Data Center
DMIS ID	Defense Medical information System Identification Number
DOD	Department of Defense
DON	Department of the Navy
EDC	EpiData Center
HA	Healthcare-associated
HAI	Healthcare-associated infection
HL7	Health Level 7
HICPAC	Hospital Infection Control Practices Advisory Committee
HO	Hospital-onset
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IV	Intravenous
M2	MHS Mart
MDR	Multidrug-resistant
MDRO	Multidrug-Resistant Organism
MEPRS	Medical Expense and Performance Reporting System
MHS	Military Health System
MTF	Military Treatment Facility
NHSN	National Healthcare Safety Network
OBS	Operation Bright Star
OCONUS	Outside of the continental United States
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OP	Outpatient
PDR	Pandrug-resistant
SHEA	The Society for Healthcare Epidemiology of America
SIDR	Standard Inpatient Data Record
SSI	Surgical site infection
UD	Unit dose
US	United States
USNS	United States Naval Ship
UTI	Urinary tract infection
VAP	Ventilator-associated pneumonia
WHO	World Health Organization
XDR	Extensively drug-resistant